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Vaginal ring for sustained release of DL-lactide as a lactic acid pro-drug

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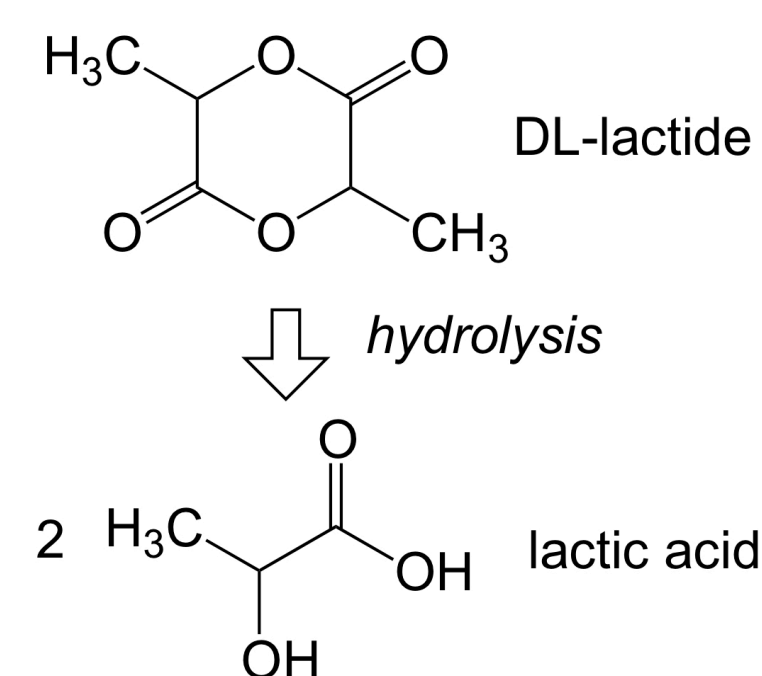
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Key points

- 1** DL-lactide, a lactic acid dimer, hydrolyses to form lactic acid. The rate constant for hydrolysis of DL-lactide at 37° C was measured as 0.05658 days⁻¹.
- 2** Lactide can be readily incorporated into a silicone elastomer vaginal ring, whereas incorporation of lactic acid inhibits the silicone elastomer curing reaction.
- 3** Lactide and lactic acid are simultaneously released from the model vaginal rings in quantities sufficient to significantly reduce and maintain low pH of simulated vaginal fluids.

Background



Maintenance of a normal vaginal microbiota is critical for vaginal health. Sexual intercourse, hormone deficiency, and use of antibiotics and contraceptives can easily disturb the population of beneficial bacteria, leading to a loss of protective lactobacilli species (which produce lactic acid), an increase in pH, and onset of vaginal infection. There is interest in developing vaginal ring products for long-acting administration of lactic acid. However, lactic acid is not compatible with silicone elastomers, the most common material for fabrication of vaginal rings. Here, we investigate the potential for controlled release of DL-lactide from a silicone elastomer vaginal ring. DL-lactide is a cyclic dimer of lactic acid and readily hydrolyses to lactic acid.

Results & Discussion

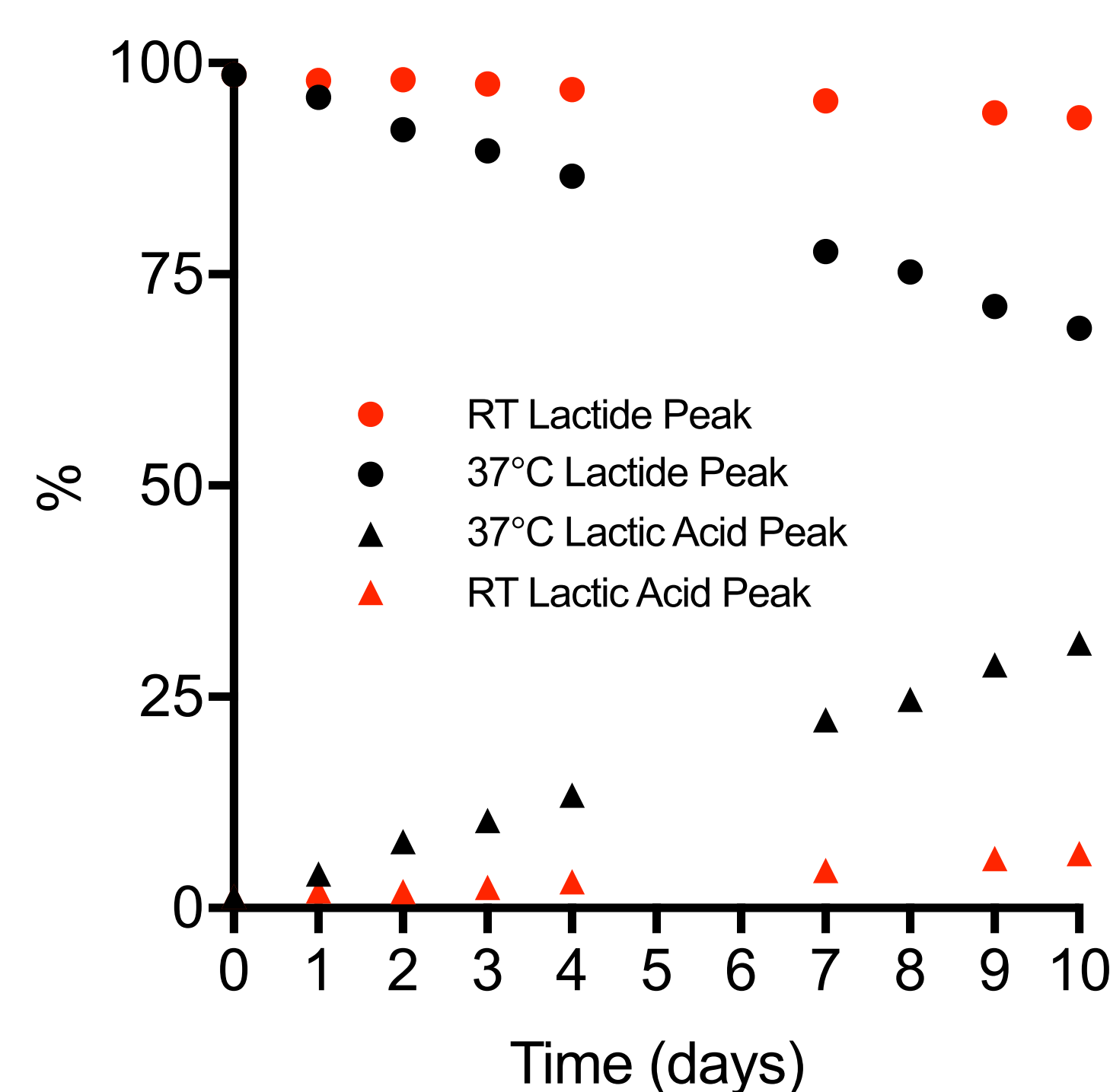


Fig. 1. Percentage conversion of lactide to lactic acid in 0.2% v/v solution of Tween over 10 days at room temperature and 37°C.

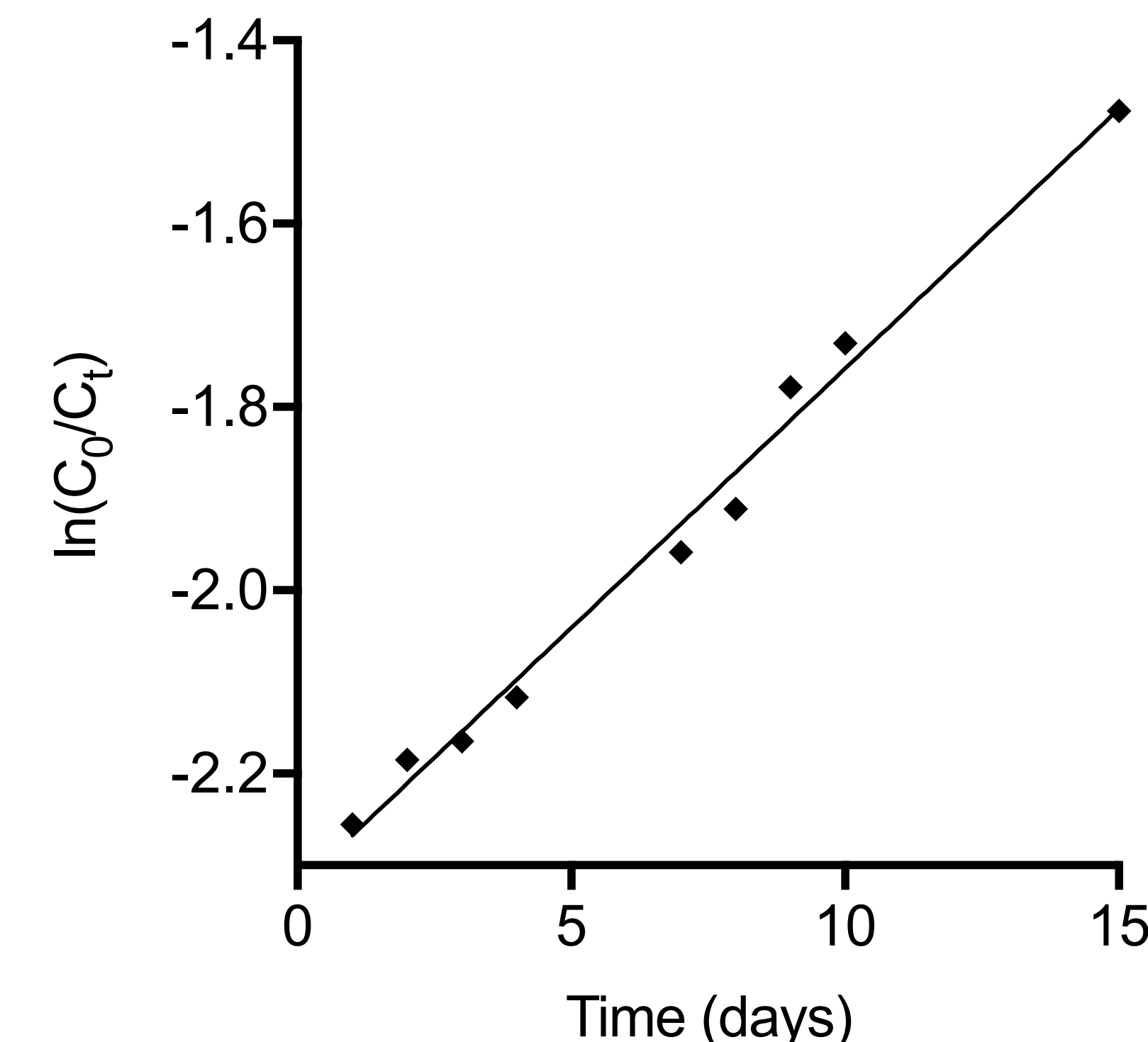


Fig. 2. Calculation of reaction rate of the hydrolysis of lactide to lactic acid at 37°C.

Unlike LA, LT was compatible with the silicone elastomer and did not inhibit cure. Hydrolysis of DL-lactide occurred in the release medium, as evidenced by the detection of lactic acid. The rate constant for hydrolysis of LT at 37° C was 0.05658 days⁻¹. pH of all replicates was substantially lowered over the release period in both pH mediums with values dropping as low as 2.75 on Day 1 for both sets of media. DL-lactide was released from the matrix-type silicone elastomer rods continuously over the 10-day period. Day 1 daily release values averaged at 20.1mg in pH 4.19 media and 28.8mg in pH 8.04 media. Day 10 values ranged from 0.2 to 0.5 mg in both pH mediums.

This proof-of-concept study demonstrated that sustained delivery of DL-lactide from a silicone elastomer vaginal ring may be helpful in lowering elevated pH in the vagina associated with bacterial infection.

Objectives

- Incorporate lactide into a silicone elastomer.
- Measure rate of hydrolysis of lactide to lactic acid at room temperature and body temperature (37°C).
- Measure in vitro release of lactide and lactic acid from model rings into simulated vaginal fluids
- Measure changes in pH of simulated vaginal fluids

Methods

Matrix-type silicone elastomer (DDU-4320) rods containing DL-lactide (11% w/w) were prepared by reaction injection molding (80°C, 3 min). *In vitro* release testing of individual rods (n=8) placed was performed over 10 days into 0.2% v/v Tween 80. The amounts of DL-lactide (LT) and lactic acid (LA) released were quantified by reverse phase UPLC. The pH of the release medium was also monitored over the release period.

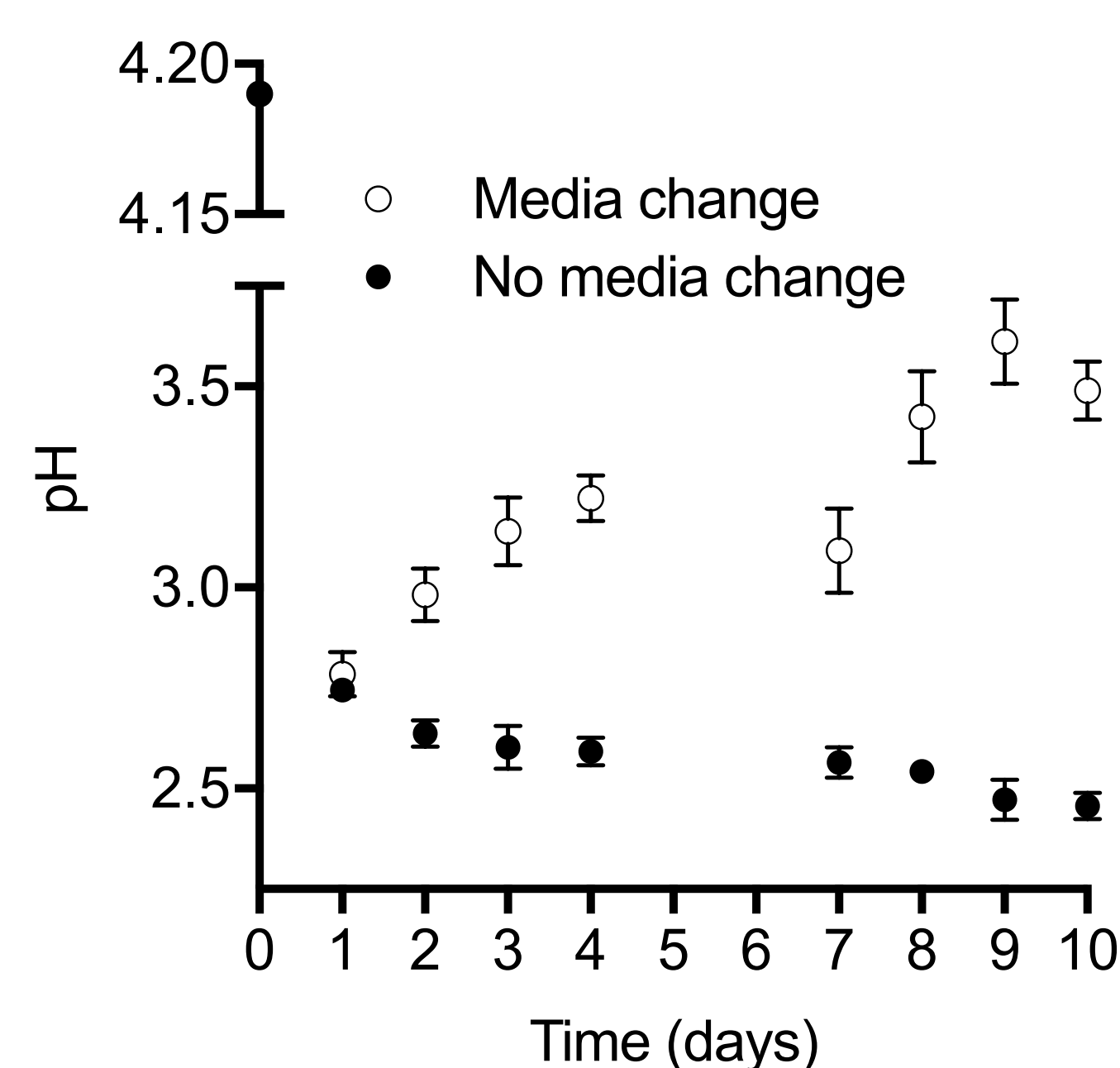


Fig. 3. pH values of 11% w/w lactide silicone rod at 37°C in 0.2% v/v solution of Tween at pH 4.19 over 10 days.

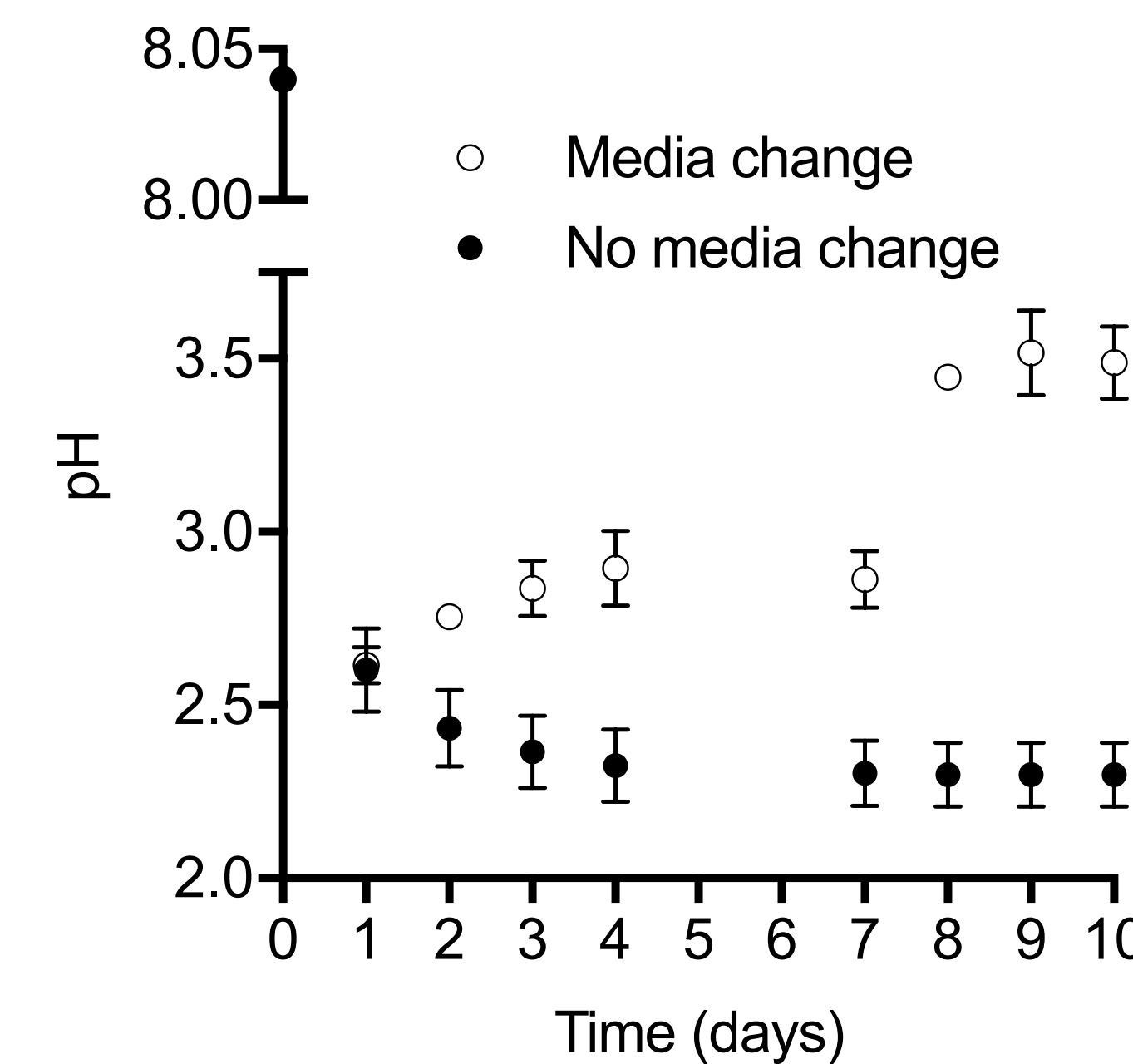


Fig. 4. pH values of 11% w/w lactide silicone rod at 37°C in 0.2% v/v solution of Tween at pH 8.04 over 10 days.

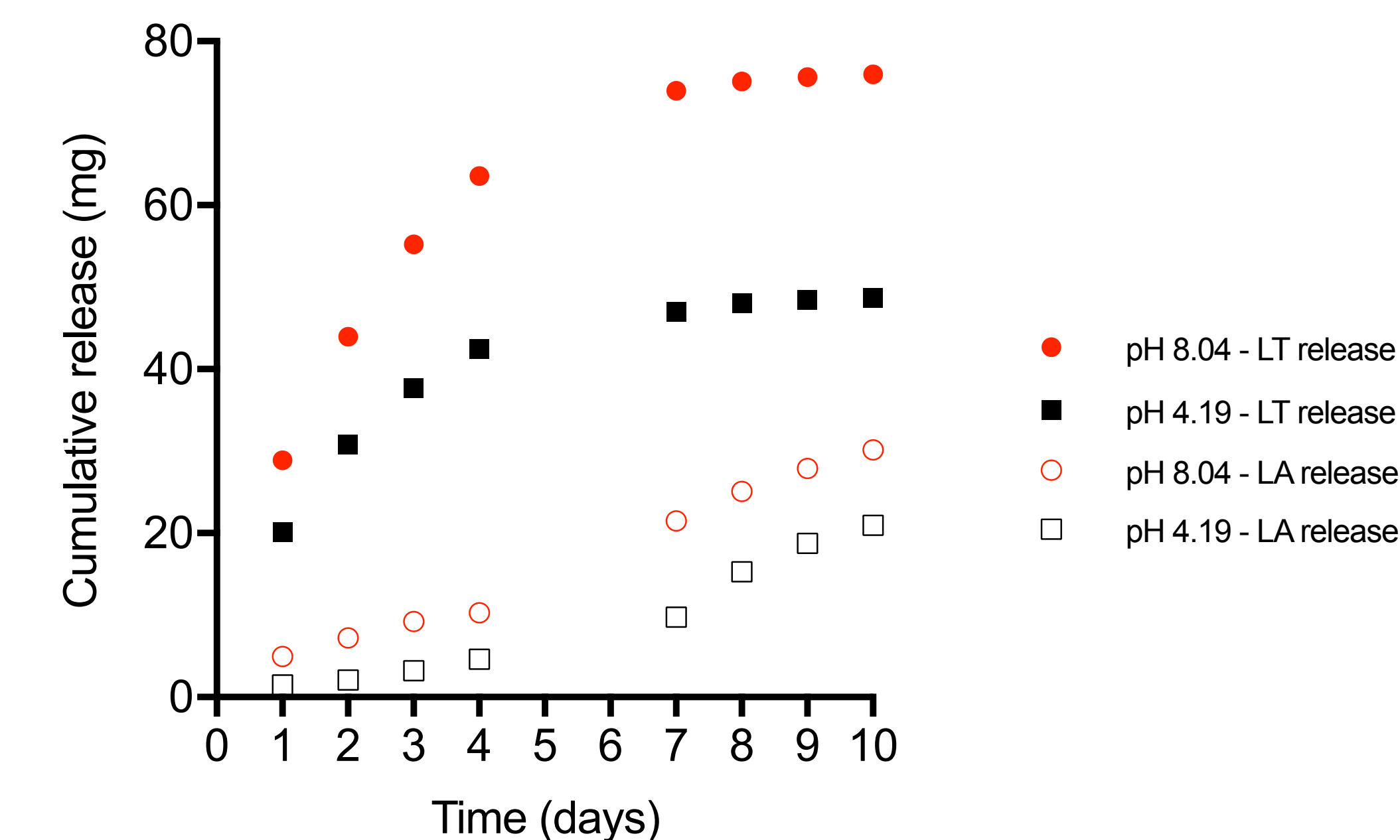


Fig. 5. Cumulative release of lactide (LT) and lactic acid (LA) at 37°C in 0.2% v/v solution of Tween at pH 4.19 and pH 8.04 over 10 days.